AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Currently Amended) A method of producing a genetically modified mammalian cell, said method comprising the steps of:

(a) inserting into one or more mammalian cells an artificial chromosome comprising a cassette which includes a first region of homology having ~~substantial~~ at least 90% sequence identity to a first region of an endogenous chromosome of said one or more mammalian ~~cell(s)~~ cells, a selectable marker, and a second region of homology having ~~substantial~~ at least 90% sequence identity to a second region of said endogenous chromosome under conditions that result in homologous recombination between said artificial chromosome and said endogenous chromosome and integration of said cassette into said endogenous chromosome of one or more mammalian cells; and

(b) selecting a mammalian cell in which said homologous recombination occurs, thereby selecting a genetically modified mammalian cell.

2. (Currently Amended) The method of claim 1, ~~wherein said artificial chromosome comprising said cassette is produced by a~~ wherein prior to step (a) said method further comprises ~~comprising~~ the ~~steps~~ step of:

~~(a)~~ culturing a host cell that has (i) a linear DNA molecule comprising said cassette and (ii) an artificial chromosome comprising a nucleic acid sequence that is ~~substantially~~ at least 90% identical to said first and second regions of homology under conditions that result in homologous recombination between said linear DNA molecule and said artificial chromosome, thereby generating ~~said~~ an artificial chromosome comprising said cassette.

3. (Original) The method of claim 2, wherein said linear DNA molecule is

introduced into said host cell by transformation.

4. (Currently Amended) The method of claim 2, wherein said linear DNA molecule is ~~introduced into~~ generated in said host cell by insertion of a circular vector comprising the sequence of said linear DNA molecule into said cell and cleavage of said vector to generate said linear DNA molecule inside said host cell.

5. (Original) The method of claim 1, wherein said first and second regions of said endogenous chromosome are contiguous.

6. (Original) The method of claim 5, wherein said first and second regions of said endogenous chromosome are part of the same exon or the same promoter.

7. (Original) The method of claim 1, wherein said first and second regions of said endogenous chromosome are not contiguous.

8. (Original) The method of claim 7, wherein said first and second regions of said endogenous chromosome are part of different exons.

9. (Currently Amended) The method of claim 1, wherein the integration of said cassette into ~~the genome~~ said endogenous chromosome of said one or more mammalian ~~cell~~ cells reduces the activity of the protein encoded by a nucleic acid of interest that includes said first or said second region of said endogenous chromosome.

10. (Currently Amended) The method of ~~claim 1~~ claim 9, wherein the amount of functional protein encoded by said nucleic acid of interest decreases by at least 25%.

11. (Currently Amended) The method of claim 1, wherein said ~~cassette comprises~~ selectable marker is a reporter gene, and wherein said cassette is integrated into ~~the genome~~ said endogenous chromosome of said one or more mammalian ~~cell~~ cells such that said reporter gene after integration is operably linked to an endogenous promoter of interest of said one or more mammalian cells, thereby generating a genetically modified mammalian cell that expresses said reporter gene under the control of said promoter.

12. (Currently Amended) The method of claim 1, wherein said ~~cassette comprises~~ selectable marker is a nucleic acid encoding a detectable protein, and wherein said cassette is integrated into ~~the genome~~ said endogenous chromosome of said one or more mammalian ~~cell~~ cells such that said nucleic acid after integration is operably linked to an endogenous nucleic acid of said one or more mammalian cells encoding a protein of interest, thereby generating a genetically modified mammalian cell that expresses a fusion protein comprising said detectable protein and protein of interest or fragment thereof.

13.-17. (Canceled)

18. (Original) The method of claim 1, wherein said mammalian cell is an embryonic stem cell.

19. (Original) The method of claim 1, wherein said mammalian cell is a somatic cell.

20.-39. (Canceled)